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This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 4/11/94 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire three (3) month(s), zero (0) days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☒ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☒ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☒ Claims 1-3 are pending in the application.

   Of the above, claims _____ are withdrawn from consideration.

2. ☐ Claims _____ have been cancelled.

3. ☐ Claims _____ are allowed.

4. ☒ Claims 1-3 are rejected.

5. ☐ Claims _____ are objected to.

6. ☐ Claims _____ are subject to restriction or election requirement.

7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.

8. ☐ Formal drawings are required in response to this Office action.

9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).

10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).

11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).

12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____ ; filed on _____.

13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.

14. ☐ Other

EXAMINER'S ACTION

This application should be reviewed for errors.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

The declaration of Dr. Chen is acknowledged, has been considered and is addressed, below.

The rejection of claims 1-31 under 35 USC 112, first paragraph, is as follows:

The argument regarding the nonenablement of the specification concerning the amount of dichloromethylene diphosphonate to administer is withdrawn in view of the submitted references; the argument regarding the limitation of the claims to non-humans is withdrawn in view of the submitted references.

The rejection of claim 31 under 35 USC 112, second paragraph, regarding the phrase "in whole or in part" is withdrawn in view of the deletion of the phrase.

The rejection of claims 1-23 and 31 under 35 USC 112, first second, regarding the word "substantially" is maintained. Applicant's arguments, filed December 26, 1996, has been considered but not found to be persuasive. Applicants have argued that the use of the word "substantially" is not indefinite. However, "at least about" is not related to "substantially" and, from the specification at page 11, only 1-10% of the administered cells remain after several days, and this does not correlate with the "substantial prevention of depletion", as claimed, since 90-99% of the cells have been depleted.

The rejection of claims 1-17 and 19-23 under 35 USC 103 as being unpatentable over Aldrovani taken with Pinto is withdrawn in view of the new grounds of rejection set forth, below.

The rejection of claim 18 under 35 USC 103 as being unpatentable over Aldrovani taken with Pinto as applied to claims 1-17 and 19-23 above and further in view of Bernstein is withdrawn in view of the new grounds of rejection set forth, below.

The rejection of claims 24-30 under 35 USC 103 as being unpatentable over Berenson and Baum taken with Pinto is withdrawn in view of the new grounds of rejection set forth, below.

The rejection of claim 31 under 35 USC 103 as being unpatentable over Baum taken with Pinto is withdrawn in view of the new grounds of rejection set forth, below.

Applicant's arguments, filed December 26, 1996, have been considered but not found to be persuasive. Applicants have argued that there is no teaching directed to the role of macrophages in the engraftment response and in transplantation generally. To that end, the examiner has additionally cited one article and one textbook showing that at the time the claimed invention was made, macrophages were known to play a role in the immune response dealing with grafted/transplanted/implanted tissues or cells. Blood and the cells contained therein are considered by those of skill in the art to be a "tissue". The claims have been rejected over the combination of the previously cited art combined with the new art. The rejections have been restated.

Applicants have argued that Aldrovani does not address the problem of rapid depletion of non-autologous hematopoietic cells. However, the "rapid depletion of non-autologous hematopoietic cells" is not seen to be different than the GVHD or other types of tissue rejection which take place upon transplantation.

Applicant's further arguments directed to the "depletion of endogenous hematopoietic cells" is seen to be an argument regarding the process of tissue rejection per se and has been addressed by the addition of a textbook reference showing that macrophages are involved in rejection of bone marrow transplants, which are transplants of hematopoietic cells. applicants' further arguments that at the time of publication of the Marcus reference it was unclear precisely which cell population or other factor(s) were responsible for rejection of non-autologous cells in engrafted SCID mice are not persuasive since Kuby discloses the

role of macrophages in tissue rejection and Pflumio discloses that macrophage activities in SCID mice are normal and may play a role in tissue rejection. The references taken as a whole clearly suggest that elimination of macrophages would eliminate or reduce their role in tissue rejection thereby prolonging or allowing acceptance of the transplanted tissue, in this case, bone marrow, containing hematopoietic stem cells, and PBLs. Pflumio provides the motivation to combine the references.

The remainder of applicant's arguments are moot in view of the teachings of Kuby that macrophages were known to be involved in tissue rejection and in view of the new grounds of rejection.

Applicants' arguments regarding the teachings of Shpitz are not persuasive since Shpitz uses monoclonal antibodies and Kuby establishes the role of macrophages in graft rejection.

Applicants' arguments addressed to the teachings of Bernstein are not persuasive. Bernstein discloses that (abstract)human monocyte-derived macrophages transfected with HIV-LTR-CAT constructs demonstrated down regulation of CAT activity after stimulation with LPS, while in contrast, fresh monocytes and the U937 cell line both demonstrated up regulation of HIV-LTR-CAT expression by LPS. Bernstein discloses that human monocyte derived macrophages infected with HIV-1 in vitro demonstrated a decrease in viral p24 release after incubation in LPS that was comparable to the negative regulation that occurred in the transient transfection assays. The previous statements regarding the teachings of Bernstein are valid. Bernstein teaches that macrophages are viral reservoirs for HIV-1 and on this basis alone it would be desirable and obvious to one of ordinary skill to deplete macrophages. Applicants have argued that "Bernstein discloses activation of monocyte derived macrophages with LPS decreases HIV replication and that, given this, the Office's statement that it would be obvious to inactivate macrophages as a method of treatment in order to abolish viral replication is

without support." However, contrary to such arguments, Bernstein discloses on page 544, column 1, first full paragraph, that macrophages with suppressed viral production may be able to escape recognition and destruction by immune defenses. Bernstein further discloses that recent evidence suggests that these cells maintain their function as antigen presenting cells which may be important in the direct transmission of HIV to CD+4 T cells. Therefore, it would have been obvious to get rid of, deplete or inactivate macrophages having suppressed viral production since those cells are apparently still viral reservoirs.

Applicants' further arguments directed to what the invention is ("...not a method of treating HIV infection, it is to treating an immunocompromised animal....") are not persuasive since the invention is not directed to treating the SCID condition, as applicants have argued ("...it is to treating an immunocompromised animal....") but is directed to treating the HIV condition in a hu-SCID mouse model.

Claims 1-17 and 19-23 are rejected under 35 U.S.C. § 103 as being unpatentable over Aldrovandi taken with Pinto, Pflumio (International Immunology, 1993) and Kuby (Immunology, 1992). Aldrovandi discloses the SCID-hu mouse as a model for HIV infection. Aldrovandi discloses that mice homozygous for the SCID genetic defect were transplanted with human fetal hematopoietic tissues and that human fetal liver and human fetal thymus transplants were infected with HIV-1. Aldrovandi discloses that the human thy/liv implants stained for both the CD4 and CD8 markers whereas the infected thy/liv implants showed a depletion of CD4+ cells. Aldrovandi further discloses that their data suggest that HIV-1 infection of the SCID-hu mouse reproduce key aspects of HIV-1 pathology in man and may be an important small animal model to study HIV-1 induced pathogenesis in vivo. Aldrovandi discloses that "The SCID-hu mouse system does not merely reproduce in vitro phenomenon, but allows infection of

primary cells to be studied in a more appropriate environment. This model may prove to be important for examining how HIV-1 infection interferes with the ontogeny of the human immune system". Aldrovandi differs from the claims in that the reference fails to disclose decreasing the number of endogenous macrophages to a level to prevent depletion of the non-autologous hematopoietic cells. However, the secondary references, Pinto et al., Pflumio and Kuby cure the deficiency. Pinto discloses that administration of dichloromethylene diphosphonate (DMDP) encapsulated in liposomes and administered intravenously will selectively deplete tissue splenic and liver macrophages. Pinto further discloses that the endogenous lymphocytes undergo leukocytosis, which is rapid proliferation of lymphocytes. Pflumio discloses (page 1510, column 1, bottom paragraph) that "Although adult mice are deficient in specific T and B cell immunity, they still posses normal levels of non-specific activities, such as natural killer cells and macrophages (reviewed in 20), that could interfere with human cell engraftment. The reduction of absence of these cellular activities in newborn SCID mice make them an attractive alternative to test as a graft recipient." Kuby discloses that macrophages are involved in allograft rejection (page 492, column 1):

"The hallmark of graft rejection involving cell mediated reactions is an influx of T lymphocytes and macrophages into the graft. Histologically, the infiltration in many cases resembles that seen during a delayed type hypersensitivity response in which lymphokines produced the T_{DTH} cells promote macrophage infiltration (see figure 13-12).",

and, (Kuby, page 494, column 1),

"Allograft rejection that is cell mediated manifests as an acute rejection of the graft beginning about 10 days after transplantation (see figure 22-2). Histopathologic examination reveals a massive infiltration of macrophages and lymphocytes at the site of tissue destruction, suggesting of TH-cell activation and proliferation".

Kuby directly discloses that macrophages are involved in graft versus host disease when the tissue transplanted is bone marrow (page 499, column 2):

"GVDH involves both an afferent phase and an efferent phase. In the afferent phase TH cells from the donor bone marrow recognize recipient peptide-MHC complexes displayed on antigen-presenting cells. Antigen presentation, together with IL-1 induces T_H activation, production of IL2 and proliferation. Cytokines elaborated by the T_H cell induce the effector phase of GVHD by activating a variety of secondary effector cells including NK cells, CTL and macrophages.The CTL may act directly to cause tissue damage in GVHD. However, cytokines such as TNF may play an even more important role in the effector phase of GVHD. TNF is released by a variety of cells including T_H cells, CTL, NK cells and macrophages. TNF has been shown to mediate direct cytolytic damage to cells. The role that TNF plays in GVHD in mice can be demonstrated by the ability of monoclonal antibody to TNF to block the development of GVHD following bone marrow transplantation in mice."

Thus, it would have been obvious to one of ordinary skill to modify the method of Aldrovandi by treating the SCID-hu mice with DMDP in order to kill the endogenous macrophages since Pinto also teaches that the DMDP liposome depletion system had been shown to diminish the humoral immune response to certain antigens in the spleen, and more importantly, had been shown to stimulate lymphocyte division. By diminishing the endogenous immune response by depleting the macrophages as suggested by Pflumio and Kuby, one of ordinary skill would have had a reasonable expectation that the autologous (human) cells of the thy/liv transplant would survive longer and would also expect a stimulation of the autologous (human) lymphocytes in view of the leukocytosis effect seen by Pinto on the endogenous lymphocytes.

Regarding claims 2 and 15, the administration of autologous cells by administration is not seen to be different than administration by transplantation since the net effect, the stimulation of leukocytosis by DMDP and simultaneous depletion of macrophages by DMDP would still result.

Regarding claim 6, the use of mice having naturally occurring low levels of macrophages would be obvious to one of ordinary skill since the purpose of the use of DMDP is to reduce the levels of macrophages.

Regarding claims 9 and 17, Aldrovandi discloses that the SCID-hu mouse infected with HIV-1 reproduces key aspects of HIV-1 pathology in man and may be an important small animal model to study HIV-1 induced pathogenesis in vivo and that the model may prove to be important for examining how HIV-1 infection interferes with the ontogeny of the human immune system. Thus, it would have been obvious to one of ordinary skill to apply the method of Aldrovandi modified by Pinto to humans having HIV infection since Pinto teaches that macrophage depletion interferes with the immune response and also stimulates lymphocyte production. Transplanted autologous T cells, or bone marrow or PBL would not be rejected in view of the teachings of Pinto the DMDP interferes with the immune response.

Regarding claims 10 and 11, ablation of the immune system to deplete the host of immune responding cells would be obvious in view of the teachings of Aldrovandi that the host must be immunocompromised (SCID) in order to allow transplantation of autologous tissue.

Regarding claims 19-23, the combination of references renders obvious the non-human mammal since Aldrovandi discloses SCID-hu mice containing human hematopoietic cells and Pinto discloses use of DMDP to inactivate macrophages.

Aldrovandi, Pflumio and Kuby provide the motivation to combine the references. Aldrovandi discloses that "The SCID-hu mouse system does not merely reproduce in vitro phenomenon, but allows infection of primary cells to be studied in a more appropriate environment. This model may prove to be important for examining how HIV-1 infection interferes with the ontogeny of the human immune system". Pflumio discloses that macrophages could

interfere with human cell engraftment and suggests using newborn mice since newborn mice have reduced or absent activities. Kuby discloses that macrophages are known in the art to be involved in graft (bone marrow) rejection. It would have been obvious in view of those teachings to treat hosts having HIV-1 infection with DMDP since DMDP is known to inactivate macrophages, a known source of HIV infection, in order to abolish a viral reservoir and maintain or prolong donor cell engraftment.

Accordingly, the modification of the method of Aldrovandi by additionally using DMDP to inactivate macrophages as suggested by Pinto, Kuby and Pflumio in order to obtain a method of preventing depletion of non-autologous hematopoietic cells was within the ordinary skill in the art at the time the claimed invention was made. From the teachings of the references, it is apparent that one of ordinary skill would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole is prima facie obvious, as evidenced by the references, especially in the absence of evidence to the contrary.

Claim 18 is rejected under 35 U.S.C. § 103 as being unpatentable over Aldrovandi and Pinto as applied to claims 1-17 and 19-23 above, and further in view of Bernstein et al. Claims 1-17 and 19-23 were rejected for reasons as stated above. Bernstein discloses (page 544, column 1 first paragraph) that macrophage growth factors such as GM-CSF, M-CSF and IL-3 may enhance HIV replication in mononuclear phagocytes and this suggests that activation of replication pathways in these cells may also be associated with viral stimulation. It would have been obvious to one of ordinary skill then to inactivate macrophages as a method of treatment in order to abolish viral replication. Bernstein therefore provides the motivation to combine the references.

Accordingly, the modification of the method of Aldrovandi, Pinto, Pflumio and Kuby by inactivating macrophages as suggested by Bernstein in order to obtain a method of treating an immunocompromised animal was within the ordinary skill in the art at the time the claimed invention was made. From the teachings of the references, it is apparent that one of ordinary skill would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole is prima facie obvious, as evidenced by the references, especially in the absence of evidence to the contrary.

Claims 24-30 are rejected under 35 U.S.C. § 103 as being unpatentable over Berenson and Baum taken with Pinto, Pflumio and Kuby. Berenson discloses administration of CD34+ marrow cells to humans having received lethal irradiation. Berenson further discloses that the CD34+ population is capable of reconstituting hematopoiesis in humans. Baum discloses that the CD34+ cell population is the hematopoietic stem cell population. Berenson and Baum differ from the claims in that the reference fails to disclose decreasing endogenous macrophages. However,the secondary references, Pinto, Pflumio and Kuby, cure the deficiency. Pinto discloses use of DMDP to inactivate the endogenous macrophages. Use of PBLs is obvious over the use of bone marrow cells since both sources would contain the CD34+ stem cells. Further, it is well known that bone marrow transplantation results in release of hematopoietic cells into the peripheral circulation of the human. CD34+ cells are stem cells and by definition are capable of reconstituting hematopoiesis in humans thereby giving rise to CD4+ T cells. The teachings of Pflumio and Kuby set forth above are incorporated herein. Pinto provides the motivation to combine the references since Pinto discloses the DMDP inactivates the macrophages, can inhibit the humoral immune response and stimulates leukocytosis. One of ordinary skill would be interested in treating and HIV patient with DMDP since DMDP

stimulates lymphocyte proliferation and HIV-1 patients are deficient in CD4+ T cells.

Accordingly, the modification of the method the method of Baum and Berenson by using DMDP as suggested by Pinto, Pflumio and Kuby in order to obtain a method of restoring hematopoietic cells to an immunocompromised human was within the ordinary skill in the art at the time the claimed invention was made. From the teachings of the references, it is apparent that one of ordinary skill would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole is prima facie obvious, as evidenced by the references, especially in the absence of evidence to the contrary.

Claim 31 is rejected under 35 U.S.C. § 103 as being unpatentable over Baum taken with Pinto, Pflumio and Kuby. Baum discloses transplantation of human bone marrow into SCID mice and identification of a human hematopoietic stem cell population. Baum differs from the claim in that the reference fails to disclose decreasing endogenous macrophages. However, the secondary references, Pinto, Kuby and Pflumio, cure the deficiency. Pinto discloses that DMDP inactivates macrophages. It would have been obvious to one of ordinary skill to modify the method of Baum by using DMDP in view of the teachings of Pinto that DMDP causes leukocytosis of lymphocytes and PMN and otherwise augments the immune responses by diminishing the humoral immune response, thereby prolonging the life of the engrafted tissue.

Accordingly, the modification of the method of Baum by using DMDP as suggested by Pinto, Kuby and Pflumio in order to obtain a method of improving engraftment efficiency was within the ordinary skill in the art at the time the claimed invention was made. From the teachings of the references, it is apparent that one of ordinary skill would have had a reasonable expectation of success in producing the claimed invention. Therefore, the

invention as a whole is prima facie obvious, as evidenced by the references, especially in the absence of evidence to the contrary.

No claim is allowed.

Papers related to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Group 1800 via the PTO FAX center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG (30 November 15, 1989). The CM1 official Fax Center number is (703) 305-3014 or (703) 305-4242.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Suzanne Ziska, Ph.D., whose telephone number is (703)308-1217. In the event the examiner is not available, the examiner's supervisor, Jasemine Chambers, Ph.D., may be contacted at phone number (703) 308-3153.

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